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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/768,917	01/24/2001	Alain P. Vicari	SF0896K	5028

24265 7590 04/16/2004

SCHERING-PLOUGH CORPORATION
PATENT DEPARTMENT (K-6-1, 1990)
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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 04/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/768,917	VICARI ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-24,27,29,31,33,35,36 and 69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-24,27,29,31,33,35,36 and 69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/30/04 has been entered. As requested, the amendment and response filed on 11/3/03, and applicant's amendment and the declaration under 37 CFR 1.132 filed concurrently with the RCE submission have been entered. Claims 21-24, 27, 29, 31, 33, 35-36, and 69 are currently pending and under examination in instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in a previous office action.

Priority

As noted in the previous office action, the instant application was filed more than twelve months after the filing date of foreign application EP 0 974 357, filed on 7/16/98. Thus, priority to EP 0 974 357 has been denied. The effective priority date of the application is the actual filing date of instant application, 1/24/01.

Claim Rejections - 35 USC § 102

The rejection of previously pending claims 21-24, 26-32, 35-36, and 69 under 35 U.S.C. 102(b) as being anticipated by WO 99/46392 (9/16/99), hereafter referred to as Kwak et al., is withdrawn in view of applicant's cancellation or amendment of the claims.

The applicant's amendment to claim 21 has resulted in the following new grounds of rejection.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 21-24, 27, 29, 31, 33, 35-36, and 69 are rejected under 35 U.S.C. 102(e) as being anticipated by US 2002/0071825 A1 (6/13/02), hereafter referred to as Schall et al.. The applicant's claims as amended recite methods of enhancing an immune response in a mammal comprising administering MCP-4 in combination with an antigen wherein the antigen and chemokine are not physically linked as a fusion protein. The applicant further claims said methods wherein the MCP-4 is administered in the form of a vector or a protein, wherein the

antigen is a tumor antigen, or viral antigen, or wherein the MCP-4 is administered intramuscularly. The applicant also claims said methods wherein a non-methylated CpG "dendritic cell activating agent" is administered with the MCP-4 and antigen.

Schall et al. teaches methods of generating immune responses in a mammal by administering an antigen and the chemotaxin human MCP-4, wherein the MCP-4 and the antigen are separate and not physically linked as a fusion protein (Schall et al., pages 13-14, 18, and 20-21). Schall et al. further teaches that the MCP-4 can be in the form of a polypeptide or a polynucleotide encoding the MCP-4 polypeptide, and that the MCP-4 can be encapsulated in liposomes, which allows for slow release (Schall et al., page 14, and page 15, paragraph 0163, and pages 20-21, claims 5, 10, 13-15, and 20-22). Schall et al. further teaches that the antigen is a tumor associated antigen such as tyrosinase, or a viral or bacteria antigen (Schall et al., pages 13-14, particularly paragraphs 0144 and 0146). Schall et al. also teaches that the compositions comprising MCP-4 and the antigen can be administered intramuscularly, intradermally, or topically (Schall et al., pages 14-15). Please note that while Schall et al. does not specifically teach that the nucleic acid vectors encoding the MCP-4 fusion protein contain unmethylated CpGs, Schall et al. does teach that the vectors can be naked DNA which is produced in bacteria (Schall et al., page 14, paragraph 0148). The presence of unmethylated CpGs in vector DNA prepared from bacteria is an inherent result of DNA replication in bacteria. Therefore, the naked DNA encoding MCP-4 taught by Schall inherently contains unmethylated CpGs. Thus, by teaching all the limitations of the claims as written, Schall et al. anticipates the instant invention as claimed.

Claim Rejections - 35 USC § 103

The rejection of pending claims 21-24, 27, 29, 31, 33, 35-36, and 69 under 35 U.S.C. 103(a) as being unpatentable over EP 0 974 357 A1 (7/16/98), hereafter referred to as Caux et al., in view of WO 98/14573 (4/9/98), hereafter referred to as Luster et al., and Dieu-Nosjean et al. (1999) J. Leuk. Biol. Vol. 66, 252-262, is maintained. Applicant's arguments and the declaration by Dr. Vicari under 37 CFR 1.132 have been fully considered but have not been found persuasive in overcoming the instant rejection of record for reasons of record discussed in detail below.

As noted in previous office actions, while the EP 0 974 357 A1 document no longer qualifies as prior art under 102(a) regarding subject matter relating to MCP-4, this document does qualify as prior art in regards to the teachings contained therein relating to other chemokines such as MIP-3α.

The applicant's arguments submitted in the after-final response regarding the teachings of Caux et al., Luster et al., and Dieu-Nosjean et al. were addressed in the advisory action mailed on 12/22/03. These comments are reiterated below.

The applicant argues that none of the cited references alone or in combination teach or suggest the claimed methods. Specifically, the applicant argues that Caux et al. may not be relied on for teaching MCP-4 and that neither Luster et al. nor Dieu-Nosjean et al. teach the combination of MCP-4 and an antigen. In response, the Office has previously acknowledged that Caux et al. may not be relied upon for teachings MCP-4. However, as stated in previous office actions, Caux et al. may be relied upon for teaching methods of using chemokines in

combination with antigens for directing the migration of antigen presenting cells, including dendritic cells, to lymphoid organs in vivo in order to increase immune responses (Caux et al., columns 4-6, and 18-19). Caux et al. teaches that the skilled artisan can use numerous different chemokines, including MIP-3α, MIP-1β, and RANTES, which are capable of attracting and/or activating antigen presenting cells to induce immune responses to antigen (Caux et al., columns 1-4). Thus, Caux et al. already provides a reasonable expectation of success in combining chemokines and antigens to stimulate immune responses. Luster et al. supplements Caux et al. by teaching the administration of human MCP-4 in the form of a protein or a nucleic acid vector in order to stimulate immune responses in a mammal (Luster et al., pages 4-5, particularly page 5, lines 9-12). Luster et al. also teaches the MCP-4 is chemotactic for antigen presenting cells such as monocytes (Luster et al., pages 34-35). Dieu-Nosjean et al. further supplements Luster et al. by teaching that MCP-4 is capable of causing the activation and migration of dendritic cells (Dieu-Nosjean et al., page 255, Table 2). Thus, based on the known properties of MCP-4 in activating and attracting dendritic cells, and stimulating immune responses, the skilled artisan would have been motivated to use MCP-4 in the methods of stimulating antigen-specific immune responses taught by Caux et al.

The applicant further argues that the inventors have shown unexpected results in the use of MCP-4 that renders the claims non-obvious. The applicant has provided evidence for "unexpected results" in the form of a declaration under 37 CFR 1.132 by Dr. Vicari, an inventor of the instant application. In the declaration, Dr. Vicari provides new data which compares the effect of MIP-3α and MCP-4 on antibody responses to β-galactosidase. Exhibit A shows that

MCP-4 appears to generate increased levels of IgG as compared to MIP-3α. Dr. Vicari states that the skilled artisan would not have expected MCP-4 to increase antibody responses to antigen based on the activity of MIP-3α. In response, the MPEP in section 716.02(d) states that in the consideration of evidence of unexpected results, "Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the 'objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support.'", citing *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980) (see also *In re Peterson*, 315 F. 3e 1325, 1329-31, 65 USPQ2d 1379, 1382-85 (Fed. Cir. 2003), and *In re Grasselli* 713 F.2d 731, 741, 218 USPQ 769, 777 (Fed. Cir. 1983)). In the instant case, the evidence provided to demonstrate "unexpected results" and thus non-obviousness is not commensurate in scope with the claims as written. The evidence provided discloses results from experiments where protein MCP-4 is administered three hours before the administration of a plasmid vector encoding the target antigen, β-galactosidase, resulting in the generation of IgG antibody generation. While the office does not dispute the applicant's evidence for higher levels of IgG obtained using MCP-4, the claims as written are not limited to the generation of humoral immune responses, but instead read broadly on the induction of immune responses in general, which may include antibody responses, but which also encompass T cell mediated responses such as cytotoxic CD4 or CD8 T cells. While the results demonstrate that MCP-4 is better than MIP-3α in increasing antigen specific antibodies, the results do not demonstrate any effect on T cell responses, or other types of immune responses. Further, it is unclear how the parameters of the experiment shown in Exhibit A have affected the results. The data was generated by sequential administration of protein MCP-4 followed by nucleic acid

immunization with the antigen. The claims are not so limited and read on the simultaneous or sequential administration of MCP-4 and antigen, and further read on administering polynucleotide MCP-4 and protein antigen. Thus, while the applicant's results demonstrate unexpected results in obtaining higher levels of antibodies following sequential administration of MCP-4 protein and a nucleic acid encoding an antigen, the results are not commensurate in scope with the scope of the claims as written.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, the technology center fax number is (703) 872-9306. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER